Abnormalities of Hippocampal Shape and Subfield Volumes in Medication-Free Patients with Obsessive-Compulsive Disorder

HUMAN BRAIN MAPPING

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Hippocampal Shape and Subfield Volumes in OCD

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Abstract

In this study, we sought to identify alterations of hippocampal shape and subfield volumes in a relatively large sample of medication-free obsessive-compulsive disorder (OCD) patients without comorbid depression. 3D T1-weighted Magnetic Resonance Imaging scans were collected from 81 medication-free OCD patients and 95 age- and sex-matched healthy controls (HC). Total hippocampal volume and volume of eight bilateral subfields were measured using FreeSurfer software. Subregional shape deformity was examined via FSL software. Volumetric and shape differences between groups and correlations with OCD symptoms were examined. The volume of right hippocampus was significantly reduced in OCD patients ($p=0.001$, $\eta^2=0.065$). Follow-up analysis of right hemisphere subfields showed reduced volume in right subiculum ($p<0.001$, $\eta^2=0.081$), presubiculum ($p<0.001$, $\eta^2=0.125$), CA2/3 ($p=0.001$, $\eta^2=0.06$) and hippocampal tail ($p<0.001$, $\eta^2=0.105$), while the volume of right fimbria was increased ($p=0.001$, $\eta^2=0.058$). Shape analysis revealed a bilateral outward bending in the hippocampal body related to a lateral displacement of hippocampus from the body to the tail. Symptom severity was correlated with volumes of presubiculum (with compulsions, $r=-0.25$, $p=0.024$) and fimbria (with obsessions, $r=-0.28$, $p=0.012$), and with the lateral shift of middle and posterior hippocampus (with obsessions). Alterations across hippocampal subfields and overall shape may contribute to the distinctive cognitive and affective abnormalities associated with OCD.

Key Words: Obsessive-compulsive Disorder, Hippocampus, Subiculum, fimbria, MRI

Introduction

Obsessive-compulsive disorder (OCD) has a lifetime population prevalence of 1-3% (Fontenelle, Mendlowicz, & Versiani, 2006) and causes significant distress and persistent functional impairment (Subramaniam, Soh, Vaingankar, Picco, & Chong, 2013). The hippocampus plays an important role in regulation of fear, stress responses and cognitive flexibility which are core domains of deficit in OCD (Bannerman et al., 2004; Milad et al., 2013; Milad & Rauch, 2012). Hippocampal-based fear extinction is impaired in patients with OCD(Milad et al., 2013; Milad & Rauch, 2012), and the hippocampal-striatal axis compromises a reward-processing system that supports flexible goal-directed behavior which is notably impaired in OCD(Gillan et al., 2011; Pennartz, Ito, Verschure, Battaglia, & Robbins, 2011; Vaghi et al., 2016). Reduced overall hippocampal volumes were reported in OCD patients in the recent multi-center ENIGMA study (Boedhoe et al., 2017; Fouche et al., 2016), but the nature of subfield specific effects determined without potential confounds of psychiatric medications or depression (that itself is associated with hippocampal changes) remains to be investigated.

Because of the anatomic and functional complexity of the structure, an analysis of hippocampal subfields may provide insights into the specific hippocampal alterations that are involved in the pathogenesis of OCD. Hippocampal subfields CA1-4 that make up the cornu ammonis (CA), the dentate gyrus (DG), subiculum, presubiculum, and the fimbria which forms the superior border of the hippocampus bear functionally differentiated roles and are histologically heterogeneous(Small, Schobel, Buxton, Witter, & Barnes, 2011). For example, the subiculum and presubiculum play roles in governing hippocampal-striatum circuitry that is crucial for generating motivated goal-directed behavior (Aggleton & Christiansen, 2015),

and functionally are important in Pavlovian fear conditioning (O'Mara, Sanchez-Vives, Brotons-Mas, & O'Hare, 2009). DG manifests the unusual feature of neurogenesis, a process by which new neurons are continuously generated through adult life. It is believed to be more vulnerable to stress-related toxic damage and depressed mood. Unique recurrent collaterals enable CA3 to generate associations between various inputs from cortex, and hence this region is important in memory processes. DG and CA3 are respectively responsible for separating (pattern separation) and summarizing (pattern completion) sensory cues in specific contexts, and are important for context-dependent memory retrieval (Knierim & Neunuebel, 2016). No volumetric analysis of hippocampal subfields in OCD has been reported with advanced, automatic image segmentation and processing techniques. Thus, a comprehensive profile of subfield-level hippocampal anatomic alterations can provide novel information regarding the relative importance of specific subfield alterations to the clinical presentation of the disorder.

The hippocampus also has a functional organization along its longitudinal axis, with the posterior hippocampus being more relevant for cognitive functions such as representing spatial information, learning and cognitive flexibility, while the anterior hippocampus plays greater roles in anxiety-related behaviors (Strange, Witter, Lein, & Moser, 2014). Thus, characterization of hippocampal alterations in OCD may benefit from analysis of overall hippocampal shape along its primary axis. One previous study used a manual segmentation and found a downward displacement in the hippocampal head(Hong et al., 2007).

In the current study, we recruited a relatively large sample OCD patients who were drug-free OCD (67 of 81 were drug-naïve) and did not have comorbid depression that might

influence hippocampal subfield and shape measurements. We addressed two primary questions. First, we applied an automated segmentation method and a vertex-based three-dimensional shape analysis to identify the specific subfield abnormalities and overall shape changes that contribute to previously reported global volume changes of the hippocampus in OCD. Second, in exploratory studies, we examined the association of identified deficits with severity of obsessive and compulsive symptoms. We hypothesized that OCD patients would demonstrate: (1) alterations in the (pre)subiculum based on its roles in both behavioral flexibility and fear conditioning; 2) alterations in CA3/DG because of its role in cognitive flexibility that is reduced in OCD; and (3) alterations in anterior hippocampus because of its role in anxiety-related behaviors.

Subjects and Methods

Subjects. This prospective study was approved by local Research Ethics Committee, and informed written consent was obtained from all participants prior to study participation. 81 medication-free OCD patients and 95 age- and sex-matched healthy controls (HC) were recruited in the present study (Table 1). All participants were right-handed and native Han Chinese. Patients were recruited from the university medical center with diagnoses established using the Structured Clinical Interview for DSM-IV disorders (SCID). Acute illness severity was assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the 14-item Hamilton Anxiety Scale (HAMA) and the 17-item Hamilton Depression Scale (HAMD).

Exclusion criteria included: (1) age less than 18 years or older than 60 years; (2) any history of affective or psychotic disorder comorbidity assessed using the SCID; (3) history of significant systemic illness, cardiovascular disease, neurological disorder, or substance abuse

or dependence; and (4) pregnancy. 67 patients were medication-naïve. The remaining 14 previously had received medication for OCD (4 clomipramine, 3 paroxetine, 3 fluoxetine, 3 sertraline and 1 with a history of treatment with 3 medications (clomipramine, paroxetine and quetiapine). Previously treated patients had been medication free for at least four weeks before MRI scans. We excluded patients with HAMD scores higher than 16 (a score that represents clinically significant depression 17) or with past or present diagnoses of depression, because depression has been associated with hippocampal changes and thus may confound efforts to identify OCD-associated hippocampal abnormalities.

HC were recruited from the local area using poster advertisements, and were screened using the SCID (non-patient version) to confirm the absence of any history of affective, psychotic or anxiety disorder. HC reported no significant history of psychiatric illness among their first-degree relatives.

Structural MRI data acquisition. MRI data were acquired using a 3.0 T MRI system and an eight-channel phase array head coil (EXCITE, General Electric, Milwaukee, WI, USA). A high resolution T1-weighted 3D Spoiled Gradient Recall sequence was used (TR=8.5 ms, TE=3.4 ms, flip angle=12°, slice thickness=1.0 mm). Field of view was 240 × 240 mm^2 with an acquisition matrix comprising 256 readings of 128 phase encoding steps that produced 156 contiguous coronal slices. The matrix size of the 3D image was automatically interpolated in-plane to 512 × 512, which yielded an in-plane resolution of 0.47 × 0.47 mm^2. Foam padding and earplugs were used to reduce head motion and scanner noise.

Volumetric analysis. Anatomic images were automatically segmented using FreeSurfer software (V. 6.0) (http://surfer.nmr.mgh.harvard.edu/). The recon-all FreeSurfer analysis pipeline was applied. Briefly, T1-weighted images were corrected for head motion, transformed into Talairach space, and signal intensity normalization and skull-strip procedures were performed(Fischl et al., 2002; Reuter, Rosas, & Fischl, 2010; Segonne et al., 2004; Sled, Zijdenbos, & Evans, 1998).

Hippocampal subfield segmentation was performed using a module in FreeSurfer software that employs a tetrahedral mesh-based probabilistic atlas built from manually delineated hippocampi using in-vivo and ex-vivo data(Iglesias et al., 2015). By this algorithm, the volume of the whole left and right hippocampus and 8 subfields were obtained, including CA1, CA2/3, CA4, granule cell layer (GCL) of the DG (GCL_DG), subiculum, presubiculum, fimbria and hippocampal tail. All segmentation was visually verified following a quality control protocol that is similar to the ENIGMA protocol (http://enigma.ini.usc.edu/). In brief, segmentation of each subject was visually checked by two co-authors independently (LZ and XH) and segmentation results judged to be incorrect were excluded (1 OCD patient).

Shape Analysis. FIRST, a model-based segmentation and registration module implemented in FSL software (version 5.0.9, https://fsl.fmrib.ox.ac.uk/), was used to automatically segment the hippocampus(Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Patenaude, Smith, Kennedy, & Jenkinson, 2011). FIRST employs shape models built from manually segmented images provided by the Center for Morphometric Analysis, MGH, Boston. Based on learned models, FIRST searches through linear combinations of shape modes of variation for the most

probable shape instance given the observed intensities in T1-weighted images(Patenaude et al., 2011). All segmentation was visually confirmed according to a similar protocol as in subfield segmentation (3 patients with OCD were excluded). Vertex data were extracted for statistical analysis.

Statistical Analysis. Multivariate analysis of covariance (MANCOVA) was used to test for overall hippocampal volume differences between groups. Step-down post-hoc t-tests were employed to test for specific subfield changes when warranted, with Bonferroni correction used to correct for multiple testing. Partial Eta Squared (η^2) was calculated to estimate effect sizes. Hemisphere by diagnosis, age by diagnosis, and gender by diagnosis interactions were examined across the whole hippocampus and subfields. Age, sex and intracranial volume (ICV) were treated as covariates in all group comparisons. Overall hippocampal volume was altered in patients, hence ICV rather than hippocampal volume was used as a covariate to correct for effects of overall brain volume in subfield analyses. A similar analysis comparing drug-naïve patients and HC revealed similar effects as seen with the full sample (see Supplementary Table 1). Potential effect of lifetime use of medication on hippocampus were also explored with a MANCOVA analysis comparing across drug-naïve patients, drug-free patients and HC (see Supplementary Table 2).

For statistical analysis of hippocampal shape data, general linear models and permutation testing used the Randomise module in FSL software(Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Threshold-Free Cluster Enhancement was used to identify clusters of voxels with significant shape deformation in OCD patients relative to HC, with the family-wise

error (FWE) rate used to control for multiple testing(Smith & Nichols, 2009).

Partial correlation analyses (age, sex, ICV adjusted) were performed to identify clinical associations of hippocampal measures that showed significant group differences with illness duration, age of onset, compulsion and obsession Y-BOCS scores, and HAMA and HAMD scores. These exploratory analyses conducted for heuristic purposes used nominal significance thresholds. To identify subfield alterations that might meaningfully contribute to shape alterations and overall hippocampal volume changes, we examined correlations between volumes of each subfield with shape and overall volume of the hippocampus.

Results

Volumetric Analysis. Whole hippocampal volume was significantly reduced in the right ($p=0.001$, $\eta^2=0.065$) but not left hemisphere ($p=0.169$, $\eta^2=0.011$) in patients with OCD relative to HC (see Table 2, Figures 1 & 2). Follow-up analyses of right hemisphere subfields revealed volume reductions in the subiculum ($p<0.001$, $\eta^2=0.081$), presubiculum ($p<0.001$, $\eta^2=0.125$), hippocampal tail ($p<0.001$, $\eta^2=0.105$), and CA2/3 ($p=0.001$, $\eta^2=0.06$). Fimbria ($p=0.001$, $\eta^2=0.058$) volume was significantly increased in OCD patients relative to HC. Significant differences were not seen in CA1, CA4 or GCL_DG.

To enable comparison of subfield effects across hemispheres, exploratory analyses of left hemisphere subfields were conducted that revealed volume reduction in hippocampal tail ($p=0.005$, $\eta^2=0.046$), CA4 ($p=0.002$, $\eta^2=0.588$) and presubiculum ($p=0.004$, $\eta^2=0.047$). Exploratory analysis at the subfield level showed significant lateralized group differences only in the fimbria ($p=0.004$, $\eta^2=0.024$). No other significant interactions were found.

In correlation analyses, we found negative correlations between compulsion scores and

volume of right presubiculum (r=-0.25, p=0.024) and between obsession scores and volume of right fimbria (r=-0.28, p=0.012). HAMA scores were negatively correlated with volume of right CA3 (r=-0.25, p=0.026). No other significant correlations were found.

Shape Analysis. Vertex-wise shape analysis revealed significant bilateral deformation in patients with OCD compared with HC after FWE correction. In both hemispheres, OCD patients demonstrated an outward bending of middle and posterior hippocampus reflecting a lateral displacement from body to tail bilaterally, giving the whole structure a more bowed appearance (vertex-wise p values are shown in Figure 3).

Modest nominally significant correlations were found between OCD symptoms and local shape deformity (Figure 4). Compulsion scores correlated with lateral displacement of the hippocampus bilaterally. Obsession scores correlated with downward displacement of right hippocampal tail.

Relationship between subfields and shape. Volumes of fimbria, subiculum and presubiculum showed the most significant correlations with hippocampal shape deformation (see Supplementary Figure 1). The volume of fimbria showed a correlation with inferolateral displacement of middle-to-posterior hippocampus bilaterally. This correlation pattern suggests that the greater the enlargement of the fimbria, the greater the lateral displacement of the hippocampal body and tail. A similar pattern was observed in the correlation between subiculum/presubiculum and shape deformity; however, these correlations were more modest and affected more restricted areas compared with those of the fimbria.

Discussion

The present study was conducted to identify regional hippocampal anatomic abnormalities in OCD patients using both shape and subfield analyses. We demonstrated reduction in specific right hemisphere hippocampal subfield volumes and bilateral subregional deformity in a relatively large group of medication-free adult OCD patients without comorbid depression.

There were two primary findings that emerged from this study. First, in OCD patients, volumes of right subiculum, presubiculum and CA2/3 were significantly reduced. Volume reduction was most prominent in presubiculum. Volume of left CA4 was reduced. These findings support our hypotheses guided by the functional properties of these subfields. In addition, we found that the volume of the right fimbria region was increased. Second, we did not find shape deformity in anterior hippocampus as predicted. Rather, we detected volume reduction in right hippocampal tail, together with a bilateral outward bend of posterior hippocampus caused by an outward/lateral displacement of the body/tail demonstrated by shape analysis. These findings provide significant clarification of OCD-related hippocampal abnormalities by clarifying the hippocampal subregions that are altered in patients with the disorder (Atmaca et al., 2008; Boedhoe et al., 2017; Fouche et al., 2016; Kwon et al., 2003). Furthermore, nominally significant correlations were found between ratings of obsession and compulsion symptom severity and some morphometric abnormalities (presubiculum, fimbria and the displacement of the tail), suggesting a clinical relevance for the identified hippocampal anatomic alterations.

We detected a volume reduction in both subiculum and presubiculum in the right hemisphere. Exploratory analysis of left hippocampus revealed reduced volume of presubiculum, and there was no significant group by hemisphere interaction, indicating that alterations in this specific subfield may not be fully restricted to the right hemisphere. Subiculum and presubiculum play an important role in gating hippocampal output to thalamus, amygdala, striatum, medial prefrontal cortex and orbitofrontal cortex(Aggleton & Christiansen, 2015), all of which are critical regions within the cortical-striatum-thalamus-cortical (CSTC) circuit that has been implicated in OCD(Menzies et al., 2008). Interactions between hippocampus and striatum are believed to generate motivational, outcome-predicting and outcome-responsive signals that invigorate flexible contextually-relevant goal-directed behaviors (Pennartz et al., 2011). Hence, dysfunction of subiculum and presubiculum may reduce the efficiency and precision of communication between hippocampus and striatum, leading to impairment in flexible goal-directed behaviors(Gillan et al., 2011; Vaghi et al., 2016) that represent a core neurocognitive feature of OCD(Gottlich, Kramer, Kordon, Hohagen, & Zurowski, 2014).

As regards subicular function, the ventral subiculum is known to play an important role in both the acquisition and extinction of Pavlovian fear conditioning(O'Mara et al., 2009). Fear extinction impairment together with diminished hippocampal response to fear conditioning have been observed in an fMRI study of OCD (Milad et al., 2013). Thus, subicular impairment may contribute to the persistence of fear responses often seen in OCD patients (Milad et al., 2013; Milad & Rauch, 2012).

Analysis of total hippocampal volumes revealed significant reduction only in right

hippocampus. Effect sizes of group differences in each hemisphere are shown in Figure 2. Overall, they indicate a more intermediate level of left hemisphere disturbance, with limited significant differences between left and right hemispheres. This lateralization profile may be related to lateralized functions of the hippocampus. In humans, the left hippocampus is specialized for language-based memories, while the right hippocampus is specialized for spatial memory(Banks, Sziklas, Sodums, & Jones-Gotman, 2012; Kesner & Rolls, 2015). Meta-analyses have revealed visuospatial memory deficits in OCD while verbal memory appears to be less impaired (Abramovitch, Abramowitz, & Mittelman, 2013; N. Y. Shin, Lee, Kim, & Kwon, 2014). Thus, the finding of lateralized subfield volume deficits in the present study may provide a neural basis for this aspect of the neuropsychological profile of OCD.

Both volumetric and shape analysis showed significant morphometric alteration in the hippocampal tail. Posterior hippocampus preferentially processes spatial information, visual memory and negative emotions(Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Satpute, Mumford, Naliboff, & Poldrack, 2012). Patients with OCD have exhibited increased activation in posterior hippocampus during a reward-based spatial learning task(Marsh et al., 2015). Thus, our anatomic findings in posterior hippocampus may be related to reward processing disturbances and negative emotions in OCD.

Analysis of hippocampal shape identified significant deformation in both the medial and lateral parts of bilateral hippocampus. This reflected a lateral displacement in central hippocampus, giving a “bowed outward” appearance to the structure. These findings differed from the only previous study investigating hippocampal shape deformity in OCD, which reported mainly a downward displacement in the hippocampal head(Hong et al., 2007). This

discrepancy may due to the smaller sample sizes (n=22) and manual segmentation used in that study together with potential differences in patient characteristics between the two studies.

Our analysis of correlations between subfield volumes and shape deformation suggests that volume increase in fimbria, the structure that constitutes the superior border of hippocampal body, may contribute to this deformation. However, fimbria is a rather small subfield compared with other subfields, and its enlargement seems unlikely on its own to cause the observed gross deformation of overall hippocampal shape (see table 2). A more plausible explanation for overall hippocampal deformation is that hypertrophy of both fimbria and perhaps also the fornix, the white matter structure that is medial to hippocampus, may be responsible for the lateral displacement of central hippocampus.

The fibers of the fimbria continue in the fornix as the fimbria-fornix complex, and act as the major output tract of the hippocampus(Saunders & Aggleton, 2007). The fimbria-fornix complex connects the hippocampus with thalamus, cingulate cortex and nucleus accumbens, all of which have been implicated in OCD (Hu et al., 2017; Menzies et al., 2008; Sudheimer et al, online atlas). Lesions of the fimbria-fornix in rodents result in resistance to behavioral extinction and thus inflexible choice behaviors. Interconnections between the hippocampus and anterior thalamus, via the fimbria-fornix complex, are especially relevant in this regard (Dumont, Amin, Wright, Dillingham, & Aggleton, 2015; Osborne, Silverhart, Markgraf, & Seggie, 1987). Whether fornix alterations contribute to hippocampal shape deformation remains to be investigated in future diffusion tensor imaging studies.

Clinical significance of the hippocampal abnormalities observed in the present study is

suggested by nominally significant correlations with behavioral ratings. We found a negative correlation between HAMA score and volume of right CA3. It has been demonstrated in animal studies that inhibition of pyramidal neurons of the dentate gyrus or CA3 is required to suppress anxiety, and that anxiety is linked to the reduction of long-term potentiation in mossy fiber-CA3 synapses which unidirectionally connect DG and CA3 (Engin et al., 2016; S. Y. Shin, Han, Woo, Jang, & Min, 2016). Thus, the identified alterations in CA3 may contribute to anxiety symptoms of OCD.

As the hippocampus is known to be pivotal for human cognition and emotion processing, it is not surprising that several psychiatric disorders have been associated with volume deficits in hippocampal subfields (Cao, Passos, Mwangi, Amaral-Silva, & Tannous, 2017; Haukvik et al., 2015; Ho et al., 2017; Maller et al., 2017; Mathew et al., 2014) using the same segmentation method as the current study. However, the pattern of subfield alterations in OCD appears to be in some ways unique. First, the relative lateralization is somewhat atypical across psychiatric disorders. Second, volume reduction of CA1 has been reported in bipolar disorder (Cao et al., 2017; Ho et al., 2017) and schizophrenia (Haukvik et al., 2015; Ho et al., 2017; Mathew et al., 2014), so its relative preservation in OCD may be a differentiating feature of the disorder. Our observation of increased volume in the fimbria has also not been reported in other psychiatric disorders. Therefore, the specific nature of hippocampal abnormalities in OCD may contribute to its distinctive clinical presentation.

There are certain limitations in the present study. First, our sample excluded those with any comorbidity or current psychiatric drug treatment. While this approach had advantages for identifying OCD-specific alterations, it remains to be determined whether our results

generalize to OCD patients with comorbid disorders and how they may be impacted by treatment. Second, although we did find modest nominal associations between symptom severity and anatomic features of the hippocampus, the effects were not large. Third, comprehensive neuropsychological testing was not completed with this sample. Future studies examining associations between subfield anatomy and the specific neurocognitive processes the subfields support may better clarify the clinical relevance of subfield-specific observations. Finally, it is possible that deformation of the hippocampus may decrease the accuracy of hippocampal segmentation, however our manual inspection of all subjects failed to identify observable software failure.

To conclude, the present study provides novel evidence of alterations in hippocampal subfield volumes in patients with OCD. The hippocampal output pathway, including fimbria, subiculum and presubiculum, was altered in OCD, suggesting a disruption in circuitry supporting communication between hippocampus and striatum that may contribute to clinical features of persistent fear and reduced behavioral flexibility in OCD. Lateralization of findings to the right hemisphere was observed, which is consistent with the neurocognitive profile of memory deficits in OCD. Future studies are needed to determine whether identified abnormalities impact functional interaction of the hippocampus with nodes of the CSTC circuit in which abnormalities have been related to OCD, and whether the observed alterations predict treatment response or are changed by successful therapy.

Data Availability Statement

The data that support the findings of this study are available form the corresponding author

upon reasonable request.

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Figure Legends

Figure 1. Bar chart of volumes of hippocampal subfields in patients with OCD compared with HC, adjusted for age, sex and ICV. *indicates significance after Bonferroni correction. Error bar indicates Standard Error. GCL_DG: Granule cell layer of the dentate gyrus.

Figure 2. Effect sizes for differences in left (grey) and right (orange) hippocampal subfields between patients with OCD and HC subjects. GCL_DG: Granule cell layer of the dentate gyrus.

Figure 3. Vertex-wise comparison of hippocampal shape between patients with OCD and healthy individuals. A. An example of hippocampal subfield segmentation by FreeSurfer (v.6.0) in a healthy subject (left hippocampus is shown). B. Left (upper line) and right (lower line) hippocampus showed a lateral displacement in body/tail, and an outward bending in the middle/posterior portion of the structure. The p values presented are corrected for multiple testing with the family-wise Error (FWE) method.

Figure 4. Vertex-wise correlation between compulsion and obsession ratings with regional shape deformity in hippocampus. Compulsions were positively correlated with lateral displacement of left (A) and right (B) hippocampus. Obsession scores were positively correlated with downward displacement of right (D) posterior hippocampus. Significance of correlations between left (C) hippocampal shape with symptom ratings did not survive Monte Carlo correction for multiple testing.

Table 1. Demographic Data and Clinical Ratings of Obsessive-Compulsive Disorder Patients (OCD) and Healthy Controls (HC)

	OCD (n=81)	HC (n=95)	P value
Age, mean (SD), years	28.4 (8.0)	28.1 (10.7)	0.836
Gender, n (% male)	50 (61.7)	59 (62.1)	0.959
Illness duration, mean (SD), years	7.0 (5.1)	NA	-
Y-BOCS score, mean (SD)	21.9 (5.4)	NA	-
Obsession score, mean (SD)	13.2 (5.2)	NA	-
Compulsion score, mean (SD)	8.7 (5.3)	NA	-
HAMA score, mean (SD)	9.1 (3.7)	NA	-
HAMD score, mean (SD)	7.9 (3.7)	NA	-

Abbreviations: OCD: Obsessive-Compulsive Disorder. HC: Healthy Control. Y-BOCS: Yale-Brown Obsessive Compulsive Scale. HAMA: Hamilton Anxiety Scale. HAMD: Hamilton Depression Scale.

Table 2 Hippocampal Subfield Volumes (mm3) in OCD Patients and Healthy Controls

	OCD (N=81) Mean (SE)	HC (N=95) Mean (SE)	F	Partial Eta Squared	P Value
Left Hippocampus					
Total volume	3239 (29)	3294 (27)	1.907	0.011	0.169
Hippocampal tail	506 (7)	535 (7)	8.243	0.046	0.005*
Presubiculum	294 (3)	308 (3)	8.471	0.047	0.004*
Subiculum	408 (5)	418 (4)	2.328	0.013	0.129
CA1	612 (7)	600 (6)	1.522	0.219	0.009
CA2/3	171 (3)	176 (2)	2.158	0.144	0.012
CA4	229 (3)	231 (2)	0.294	0.588	0.002*
GCL_DG	270 (5)	272 (3)	0.193	0.001	0.661
Fimbria	92 (2)	94 (2)	0.687	0.408	0.004*
Right Hippocampus					
Total volume	3217 (31)	3363 (29)	11.831	0.065	0.001*
Hippocampal tail	480 (8)	528 (7)	20.043	0.105	<0.001*
Presubiculum	270 (4)	294 (3)	24.365	0.125	<0.001*
Subiculum	395 (5)	420 (4)	15.172	0.081	<0.001*
CA1	638 (7)	639 (7)	0.017	0.000	0.896
CA2/3	179 (3)	191 (2)	10.995	0.060	0.001*
CA4	229 (3)	239 (2)	7.410	0.042	0.007
GCL_DG	270 (3)	281 (3)	6.542	0.037	0.011
Fimbria	97 (2)	89 (2)	10.563	0.058	0.001*

Abbreviations: * Significant after correction for multiple testing with Bonferroni method. P values are presented before Bonferroni correction. GCL_DG: Granule cell layer (GCL) of the Dentate Gyrus. Data presented include means and SEM.

Title page

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Abnormalities of Hippocampal Shape and Subfield Volumes in Medication-Free Patients with Obsessive-Compulsive Disorder

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Hippocampal Shape and Subfield Volumes in OCD

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Abstract

In this study, we sought to identify alterations of hippocampal shape and subfield volumes in a relatively large sample of medication-free obsessive-compulsive disorder (OCD) patients without comorbid depression. 3D T1-weighted Magnetic Resonance Imaging scans were collected from 81 medication-free OCD patients and 95 age- and sex-matched healthy controls (HC). Total hippocampal volume and volume of eight bilateral subfields were measured using FreeSurfer software. Subregional shape deformity was examined via FSL software. Volumetric and shape differences between groups and correlations with OCD symptoms were examined. The volume of right hippocampus was significantly reduced in OCD patients ($p=0.001$, $\eta^2=0.065$). Follow-up analysis of right hemisphere subfields showed reduced volume in right subiculum ($p<0.001$, $\eta^2=0.081$), presubiculum ($p<0.001$, $\eta^2=0.125$), CA2/3 ($p=0.001$, $\eta^2=0.06$) and hippocampal tail ($p<0.001$, $\eta^2=0.105$), while the volume of right fimbria was increased ($p=0.001$, $\eta^2=0.058$). Shape analysis revealed a bilateral outward bending in the hippocampal body related to a lateral displacement of hippocampus from the body to the tail. Symptom severity was correlated with volumes of presubiculum (with compulsions, $r=-0.25$, $p=0.024$) and fimbria (with obsessions, $r=-0.28$, $p=0.012$), and with the lateral shift of middle and posterior hippocampus (with obsessions). Alterations across hippocampal subfields and overall shape may contribute to the distinctive cognitive and affective abnormalities associated with OCD.

Key Words: Obsessive-compulsive Disorder, Hippocampus, Subiculum, fimbria, MRI

Introduction

Obsessive-compulsive disorder (OCD) has a lifetime population prevalence of 1-3% (Fontenelle, Mendlowicz, & Versiani, 2006) and causes significant distress and persistent functional impairment (Subramaniam, Soh, Vaingankar, Picco, & Chong, 2013). The hippocampus plays an important role in regulation of fear, stress responses and cognitive flexibility which are core domains of deficit in OCD (Bannerman et al., 2004; Milad et al., 2013; Milad & Rauch, 2012). Hippocampal-based fear extinction is impaired in patients with OCD(Milad et al., 2013; Milad & Rauch, 2012), and the hippocampal-striatal axis compromises a reward-processing system that supports flexible goal-directed behavior which is notably impaired in OCD(Gillan et al., 2011; Pennartz, Ito, Verschure, Battaglia, & Robbins, 2011; Vaghi et al., 2016). Reduced overall hippocampal volumes were reported in OCD patients in the recent multi-center ENIGMA study (Boedhoe et al., 2017; Fouche et al., 2016), but the nature of subfield specific effects determined without potential confounds of psychiatric medications or depression (that itself is associated with hippocampal changes) remains to be investigated.

Because of the anatomic and functional complexity of the structure, an analysis of hippocampal subfields may provide insights into the specific hippocampal alterations that are involved in the pathogenesis of OCD. Hippocampal subfields CA1-4 that make up the cornu ammonis (CA), the dentate gyrus (DG), subiculum, presubiculum, and the fimbria which forms the superior border of the hippocampus bear functionally differentiated roles and are histologically heterogeneous(Small, Schobel, Buxton, Witter, & Barnes, 2011). For example, the subiculum and presubiculum play roles in governing hippocampal-striatum circuitry that is crucial for generating motivated goal-directed behavior (Aggleton & Christiansen, 2015),

and functionally are important in Pavlovian fear conditioning (O'Mara, Sanchez-Vives, Brotons-Mas, & O'Hare, 2009). DG manifests the unusual feature of neurogenesis, a process by which new neurons are continuously generated through adult life. It is believed to be more vulnerable to stress-related toxic damage and depressed mood. Unique recurrent collaterals enable CA3 to generate associations between various inputs from cortex, and hence this region is important in memory processes. DG and CA3 are respectively responsible for separating (pattern separation) and summarizing (pattern completion) sensory cues in specific contexts, and are important for context-dependent memory retrieval (Knierim & Neunuebel, 2016). No volumetric analysis of hippocampal subfields in OCD has been reported with advanced, automatic image segmentation and processing techniques. Thus, a comprehensive profile of subfield-level hippocampal anatomic alterations can provide novel information regarding the relative importance of specific subfield alterations to the clinical presentation of the disorder.

The hippocampus also has a functional organization along its longitudinal axis, with the posterior hippocampus being more relevant for cognitive functions such as representing spatial information, learning and cognitive flexibility, while the anterior hippocampus plays greater roles in anxiety-related behaviors (Strange, Witter, Lein, & Moser, 2014). Thus, characterization of hippocampal alterations in OCD may benefit from analysis of overall hippocampal shape along its primary axis. One previous study used a manual segmentation and found a downward displacement in the hippocampal head(Hong et al., 2007).

In the current study, we recruited a relatively large sample OCD patients who were drug-free OCD (67 of 81 were drug-naïve) and did not have comorbid depression that might

influence hippocampal subfield and shape measurements. We addressed two primary questions. First, we applied an automated segmentation method and a vertex-based three-dimensional shape analysis to identify the specific subfield abnormalities and overall shape changes that contribute to previously reported global volume changes of the hippocampus in OCD. Second, in exploratory studies, we examined the association of identified deficits with severity of obsessive and compulsive symptoms. We hypothesized that OCD patients would demonstrate: (1) alterations in the (pre)subiculum based on its roles in both behavioral flexibility and fear conditioning; 2) alterations in CA3/DG because of its role in cognitive flexibility that is reduced in OCD; and (3) alterations in anterior hippocampus because of its role in anxiety-related behaviors.

Subjects and Methods

Subjects. This prospective study was approved by local Research Ethics Committee, and informed written consent was obtained from all participants prior to study participation. 81 medication-free OCD patients and 95 age- and sex-matched healthy controls (HC) were recruited in the present study (Table 1). All participants were right-handed and native Han Chinese. Patients were recruited from the university medical center with diagnoses established using the Structured Clinical Interview for DSM-IV disorders (SCID). Acute illness severity was assessed using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the 14-item Hamilton Anxiety Scale (HAMA) and the 17-item Hamilton Depression Scale (HAMD).

Exclusion criteria included: (1) age less than 18 years or older than 60 years; (2) any history of affective or psychotic disorder comorbidity assessed using the SCID; (3) history of significant systemic illness, cardiovascular disease, neurological disorder, or substance abuse

or dependence; and (4) pregnancy. 67 patients were medication-naïve. The remaining 14 previously had received medication for OCD (4 clomipramine, 3 paroxetine, 3 fluoxetine, 3 sertraline and 1 with a history of treatment with 3 medications (clomipramine, paroxetine and quetiapine). Previously treated patients had been medication free for at least four weeks before MRI scans. We excluded patients with HAMD scores higher than 16 (a score that represents clinically significant depression 17) or with past or present diagnoses of depression, because depression has been associated with hippocampal changes and thus may confound efforts to identify OCD-associated hippocampal abnormalities.

HC were recruited from the local area using poster advertisements, and were screened using the SCID (non-patient version) to confirm the absence of any history of affective, psychotic or anxiety disorder. HC reported no significant history of psychiatric illness among their first-degree relatives.

Structural MRI data acquisition. MRI data were acquired using a 3.0 T MRI system and an eight-channel phase array head coil (EXCITE, General Electric, Milwaukee, WI, USA). A high resolution T1-weighted 3D Spoiled Gradient Recall sequence was used (TR=8.5 ms, TE=3.4 ms, flip angle=12°, slice thickness=1.0 mm). Field of view was 240 × 240 mm^2 with an acquisition matrix comprising 256 readings of 128 phase encoding steps that produced 156 contiguous coronal slices. The matrix size of the 3D image was automatically interpolated in-plane to 512 × 512, which yielded an in-plane resolution of 0.47 × 0.47 mm^2. Foam padding and earplugs were used to reduce head motion and scanner noise.

Volumetric analysis. Anatomic images were automatically segmented using FreeSurfer software (V. 6.0) (http://surfer.nmr.mgh.harvard.edu/). The recon-all FreeSurfer analysis pipeline was applied. Briefly, T1-weighted images were corrected for head motion, transformed into Talairach space, and signal intensity normalization and skull-strip procedures were performed(Fischl et al., 2002; Reuter, Rosas, & Fischl, 2010; Segonne et al., 2004; Sled, Zijdenbos, & Evans, 1998).

Hippocampal subfield segmentation was performed using a module in FreeSurfer software that employs a tetrahedral mesh-based probabilistic atlas built from manually delineated hippocampi using in-vivo and ex-vivo data(Iglesias et al., 2015). By this algorithm, the volume of the whole left and right hippocampus and 8 subfields were obtained, including CA1, CA2/3, CA4, granule cell layer (GCL) of the DG (GCL_DG), subiculum, presubiculum, fimbria and hippocampal tail. All segmentation was visually verified following a quality control protocol that is similar to the ENIGMA protocol (http://enigma.ini.usc.edu/). In brief, segmentation of each subject was visually checked by two co-authors independently (LZ and XH) and segmentation results judged to be incorrect were excluded **(1 OCD patient)**.

Shape Analysis. FIRST, a model-based segmentation and registration module implemented in FSL software (version 5.0.9, https://fsl.fmrib.ox.ac.uk/), was used to automatically segment the hippocampus(Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Patenaude, Smith, Kennedy, & Jenkinson, 2011). FIRST employs shape models built from manually segmented images provided by the Center for Morphometric Analysis, MGH, Boston. Based on learned models, FIRST searches through linear combinations of shape modes of variation for the most

probable shape instance given the observed intensities in T1-weighted images(Patenaude et al., 2011). All segmentation was visually confirmed according to a similar protocol as in subfield segmentation **(3 patients with OCD were excluded)**. Vertex data were extracted for statistical analysis.

Statistical Analysis. Multivariate analysis of covariance (MANCOVA) was used to test for overall hippocampal volume differences between groups. Step-down post-hoc t-tests were employed to test for specific subfield changes when warranted, with Bonferroni correction used to correct for multiple testing. Partial Eta Squared (η^2) was calculated to estimate effect sizes. Hemisphere by diagnosis, age by diagnosis, and gender by diagnosis interactions were examined across the whole hippocampus and subfields. Age, sex and intracranial volume (ICV) were treated as covariates in all group comparisons. Overall hippocampal volume was altered in patients, hence ICV rather than hippocampal volume was used as a covariate to correct for effects of overall brain volume in subfield analyses. A similar analysis comparing drug-naïve patients, **drug-free patients** and HC revealed similar effects as seen with the full sample (see Supplementary Table 1). **Potential effect of lifetime use of medication on hippocampus were also explored with a MANCOVA analysis comparing across drug-naïve patients, drug-free patients and HC (see Supplementary Table 2).**

For statistical analysis of hippocampal shape data, general linear models and permutation testing used the Randomise module in FSL software(Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Threshold-Free Cluster Enhancement was used to identify clusters of voxels with significant shape deformation in OCD patients relative to HC, with the family-wise

error (FWE) rate used to control for multiple testing(Smith & Nichols, 2009).

Partial correlation analyses (age, sex, ICV adjusted) were performed to identify clinical associations of hippocampal measures that showed significant group differences with illness duration, age of onset, compulsion and obsession Y-BOCS scores, and HAMA and HAMD scores. These exploratory analyses conducted for heuristic purposes used nominal significance thresholds. To identify subfield alterations that might meaningfully contribute to shape alterations and overall hippocampal volume changes, we examined correlations between volumes of each subfield with shape and overall volume of the hippocampus.

Results

Volumetric Analysis. Whole hippocampal volume was significantly reduced in the right ($p=0.001$, $\eta^2=0.065$) but not left hemisphere ($p=0.169$, $\eta^2=0.011$) in patients with OCD relative to HC (see Table 2, Figures 1 & 2). Follow-up analyses of right hemisphere subfields revealed volume reductions in the subiculum ($p<0.001$, $\eta^2=0.081$), presubiculum ($p<0.001$, $\eta^2=0.125$), hippocampal tail ($p<0.001$, $\eta^2=0.105$), and CA2/3 ($p=0.001$, $\eta^2=0.06$). Fimbria ($p=0.001$, $\eta^2=0.058$) volume was significantly increased in OCD patients relative to HC. Significant differences were not seen in CA1, CA4 or GCL_DG.

To enable comparison of subfield effects across hemispheres, exploratory analyses of left hemisphere subfields were conducted that revealed volume reduction in hippocampal tail ($p=0.005$, $\eta^2=0.046$), CA4 ($p=0.002$, $\eta^2=0.588$) and presubiculum ($p=0.004$, $\eta^2=0.047$). Exploratory analysis at the subfield level showed significant lateralized group differences only in the fimbria ($p=0.004$, $\eta^2=0.024$). No other significant interactions were found.

In correlation analyses, we found negative correlations between compulsion scores and

volume of right presubiculum (r=-0.25, p=0.024) and between obsession scores and volume of right fimbria (r=-0.28, p=0.012). HAMA scores were negatively correlated with volume of right CA3 (r=-0.25, p=0.026). No other significant correlations were found.

Shape Analysis. Vertex-wise shape analysis revealed significant bilateral deformation in patients with OCD compared with HC after FWE correction. In both hemispheres, OCD patients demonstrated an outward bending of middle and posterior hippocampus reflecting a lateral displacement from body to tail bilaterally, giving the whole structure a more bowed appearance (vertex-wise p values are shown in Figure 3).

Modest nominally significant correlations were found between OCD symptoms and local shape deformity (Figure 4). Compulsion scores correlated with lateral displacement of the hippocampus bilaterally. Obsession scores correlated with downward displacement of right hippocampal tail.

Relationship between subfields and shape. Volumes of fimbria, subiculum and presubiculum showed the most significant correlations with hippocampal shape deformation (see Supplementary Figure 1). The volume of fimbria showed a correlation with inferolateral displacement of middle-to-posterior hippocampus bilaterally. This correlation pattern suggests that the greater the enlargement of the fimbria, the greater the lateral displacement of the hippocampal body and tail. A similar pattern was observed in the correlation between subiculum/presubiculum and shape deformity; however, these correlations were more modest and affected more restricted areas compared with those of the fimbria.

Discussion

The present study was conducted to identify regional hippocampal anatomic abnormalities in OCD patients using both shape and subfield analyses. We demonstrated reduction in specific right hemisphere hippocampal subfield volumes and bilateral subregional deformity in a relatively large group of medication-free adult OCD patients without comorbid depression.

There were two primary findings that emerged from this study. First, in OCD patients, volumes of right subiculum, presubiculum and CA2/3 were significantly reduced. Volume reduction was most prominent in presubiculum. Volume of left CA4 was reduced. These findings support our hypotheses guided by the functional properties of these subfields. In addition, we found that the volume of the right fimbria region was increased. Second, we did not find shape deformity in anterior hippocampus as predicted. Rather, we detected volume reduction in right hippocampal tail, together with a bilateral outward bend of posterior hippocampus caused by an outward/lateral displacement of the body/tail demonstrated by shape analysis. These findings provide significant clarification of OCD-related hippocampal abnormalities by clarifying the hippocampal subregions that are altered in patients with the disorder (Atmaca et al., 2008; Boedhoe et al., 2017; Fouche et al., 2016; Kwon et al., 2003). Furthermore, nominally significant correlations were found between ratings of obsession and compulsion symptom severity and some morphometric abnormalities **(presubiculum, fimbria and the displacement of the tail)**, suggesting a clinical relevance for the identified hippocampal anatomic alterations.

We detected a volume reduction in both subiculum and presubiculum in the right hemisphere. Exploratory analysis of left hippocampus revealed reduced volume of presubiculum, and there was no significant group by hemisphere interaction, indicating that alterations in this specific subfield may not be fully restricted to the right hemisphere. Subiculum and presubiculum play an important role in gating hippocampal output to thalamus, amygdala, striatum, medial prefrontal cortex and orbitofrontal cortex(Aggleton & Christiansen, 2015), all of which are critical regions within the cortical-striatum-thalamus-cortical (CSTC) circuit that has been implicated in OCD(Menzies et al., 2008). Interactions between hippocampus and striatum are believed to generate motivational, outcome-predicting and outcome-responsive signals that invigorate flexible contextually-relevant goal-directed behaviors (Pennartz et al., 2011). Hence, dysfunction of subiculum and presubiculum may reduce the efficiency and precision of communication between hippocampus and striatum, leading to impairment in flexible goal-directed behaviors(Gillan et al., 2011; Vaghi et al., 2016) that represent a core neurocognitive feature of OCD(Gottlich, Kramer, Kordon, Hohagen, & Zurowski, 2014).

As regards subicular function, the ventral subiculum is known to play an important role in both the acquisition and extinction of Pavlovian fear conditioning(O'Mara et al., 2009). Fear extinction impairment together with diminished hippocampal response to fear conditioning have been observed in an fMRI study of OCD (Milad et al., 2013). Thus, subicular impairment may contribute to the persistence of fear responses often seen in OCD patients (Milad et al., 2013; Milad & Rauch, 2012).

Analysis of total hippocampal volumes revealed significant reduction only in right

hippocampus. Effect sizes of group differences in each hemisphere are shown in Figure 2. Overall, they indicate a more intermediate level of left hemisphere disturbance, with limited significant differences between left and right hemispheres. This lateralization profile may be related to lateralized functions of the hippocampus. In humans, the left hippocampus is specialized for language-based memories, while the right hippocampus is specialized for spatial memory(Banks, Sziklas, Sodums, & Jones-Gotman, 2012; Kesner & Rolls, 2015). Meta-analyses have revealed visuospatial memory deficits in OCD while verbal memory appears to be less impaired (Abramovitch, Abramowitz, & Mittelman, 2013; N. Y. Shin, Lee, Kim, & Kwon, 2014). Thus, the finding of lateralized subfield volume deficits in the present study may provide a neural basis for this aspect of the neuropsychological profile of OCD.

Both volumetric and shape analysis showed significant morphometric alteration in the hippocampal tail. Posterior hippocampus preferentially processes spatial information, visual memory and negative emotions(Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Satpute, Mumford, Naliboff, & Poldrack, 2012). Patients with OCD have exhibited increased activation in posterior hippocampus during a reward-based spatial learning task(Marsh et al., 2015). Thus, our anatomic findings in posterior hippocampus may be related to reward processing disturbances and negative emotions in OCD.

Analysis of hippocampal shape identified significant deformation in both the medial and lateral parts of bilateral hippocampus. This reflected a lateral displacement in central hippocampus, giving a “bowed outward” appearance to the structure. These findings differed from the only previous study investigating hippocampal shape deformity in OCD, which reported mainly a downward displacement in the hippocampal head(Hong et al., 2007). This

discrepancy may due to the smaller sample sizes (n=22) and manual segmentation used in that study together with potential differences in patient characteristics between the two studies.

Our analysis of correlations between subfield volumes and shape deformation suggests that volume increase in fimbria, the structure that constitutes the superior border of hippocampal body, may contribute to this deformation. However, fimbria is a rather small subfield compared with other subfields, and its enlargement seems unlikely on its own to cause the observed gross deformation of overall hippocampal shape (see table 2). A more plausible explanation for overall hippocampal deformation is that hypertrophy of both fimbria and perhaps also the fornix, the white matter structure that is medial to hippocampus, may be responsible for the lateral displacement of central hippocampus.

The fibers of the fimbria continue in the fornix as the fimbria-fornix complex, and act as the major output tract of the hippocampus(Saunders & Aggleton, 2007). The fimbria-fornix complex connects the hippocampus with thalamus, cingulate cortex and nucleus accumbens, all of which have been implicated in OCD (Hu et al., 2017; Menzies et al., 2008; Sudheimer et al, online atlas). Lesions of the fimbria-fornix in rodents result in resistance to behavioral extinction and thus inflexible choice behaviors. Interconnections between the hippocampus and anterior thalamus, via the fimbria-fornix complex, are especially relevant in this regard (Dumont, Amin, Wright, Dillingham, & Aggleton, 2015; Osborne, Silverhart, Markgraf, & Seggie, 1987). Whether fornix alterations contribute to hippocampal shape deformation remains to be investigated in future diffusion tensor imaging studies.

Clinical significance of the hippocampal abnormalities observed in the present study is

suggested by nominally significant correlations with behavioral ratings. We found a negative correlation between HAMA score and volume of right CA3. It has been demonstrated in animal studies that inhibition of pyramidal neurons of the dentate gyrus or CA3 is required to suppress anxiety, and that anxiety is linked to the reduction of long-term potentiation in mossy fiber-CA3 synapses which unidirectionally connect DG and CA3 (Engin et al., 2016; S. Y. Shin, Han, Woo, Jang, & Min, 2016). Thus, the identified alterations in CA3 may contribute to anxiety symptoms of OCD.

As the hippocampus is known to be pivotal for human cognition and emotion processing, it is not surprising that several psychiatric disorders have been associated with volume deficits in hippocampal subfields (Cao, Passos, Mwangi, Amaral-Silva, & Tannous, 2017; Haukvik et al., 2015; Ho et al., 2017; Maller et al., 2017; Mathew et al., 2014) using the same segmentation method as the current study. However, the pattern of subfield alterations in OCD appears to be in some ways unique. First, the relative lateralization is somewhat atypical across psychiatric disorders. Second, volume reduction of CA1 has been reported in bipolar disorder (Cao et al., 2017; Ho et al., 2017) and schizophrenia (Haukvik et al., 2015; Ho et al., 2017; Mathew et al., 2014), so its relative preservation in OCD may be a differentiating feature of the disorder. Our observation of increased volume in the fimbria has also not been reported in other psychiatric disorders. Therefore, the specific nature of hippocampal abnormalities in OCD may contribute to its distinctive clinical presentation.

There are certain limitations in the present study. First, our sample excluded those with any comorbidity or current psychiatric drug treatment. While this approach had advantages for identifying OCD-specific alterations, it remains to be determined whether our results

generalize to OCD patients with comorbid disorders and how they may be impacted by treatment. Second, although we did find modest nominal associations between symptom severity and anatomic features of the hippocampus, the effects were not large. Third, comprehensive neuropsychological testing was not completed with this sample. Future studies examining associations between subfield anatomy and the specific neurocognitive processes the subfields support may better clarify the clinical relevance of subfield-specific observations. Finally, it is possible that deformation of the hippocampus may decrease the accuracy of hippocampal segmentation, however our manual inspection of all subjects failed to identify observable software failure.

To conclude, the present study provides novel evidence of alterations in hippocampal subfield volumes in patients with OCD. The hippocampal output pathway, including fimbria, subiculum and presubiculum, was altered in OCD, suggesting a disruption in circuitry supporting communication between hippocampus and striatum that may contribute to clinical features of persistent fear and reduced behavioral flexibility in OCD. Lateralization of findings to the right hemisphere was observed, which is consistent with the neurocognitive profile of memory deficits in OCD. Future studies are needed to determine whether identified abnormalities impact functional interaction of the hippocampus with nodes of the CSTC circuit in which abnormalities have been related to OCD, and whether the observed alterations predict treatment response or are changed by successful therapy.

Data Availability Statement

The data that support the findings of this study are available form the corresponding author

upon reasonable request.

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Figure Legends

Figure 1. Bar chart of volumes of hippocampal subfields in patients with OCD compared with HC, adjusted for age, sex and ICV. *indicates significance after Bonferroni correction. Error bar indicates Standard Error. GCL_DG: Granule cell layer of the dentate gyrus.

Figure 2. Effect sizes for differences in left (grey) and right (orange) hippocampal subfields between patients with OCD and HC subjects. GCL_DG: Granule cell layer of the dentate gyrus.

Figure 3. Vertex-wise comparison of hippocampal shape between patients with OCD and healthy individuals. A. An example of hippocampal subfield segmentation by FreeSurfer (v.6.0) in a healthy subject (left hippocampus is shown). B. Left (upper line) and right (lower line) hippocampus showed a lateral displacement in body/tail, and an outward bending in the middle/posterior portion of the structure. The p values presented are corrected for multiple testing with the family-wise Error (FWE) method.

Figure 4. Vertex-wise correlation between compulsion and obsession ratings with regional shape deformity in hippocampus. Compulsions were positively correlated with lateral displacement of left (A) and right (B) hippocampus. Obsession scores were positively correlated with downward displacement of right (D) posterior hippocampus. Significance of correlations between left (C) hippocampal shape with symptom ratings did not survive Monte Carlo correction for multiple testing.

Table 1. Demographic Data and Clinical Ratings of Obsessive-Compulsive Disorder Patients (OCD) and Healthy Controls (HC)

	OCD (n=81)	HC (n=95)	P value
Age, mean (SD), years	28.4 (8.0)	28.1 (10.7)	0.836
Gender, n (% male)	50 (61.7)	59 (62.1)	0.959
Illness duration, mean (SD), years	7.0 (5.1)	NA	-
Y-BOCS score, mean (SD)	21.9 (5.4)	NA	-
Obsession score, mean (SD)	13.2 (5.2)	NA	-
Compulsion score, mean (SD)	8.7 (5.3)	NA	-
HAMA score, mean (SD)	9.1 (3.7)	NA	-
HAMD score, mean (SD)	7.9 (3.7)	NA	-

Abbreviations: OCD: Obsessive-Compulsive Disorder. HC: Healthy Control. Y-BOCS: Yale-Brown Obsessive Compulsive Scale. HAMA: Hamilton Anxiety Scale. HAMD: Hamilton Depression Scale.

Table 2 Hippocampal Subfield Volumes (mm3) in OCD Patients and Healthy Controls

	OCD (N=81) Mean (SE)	HC (N=95) Mean (SE)	F	Partial Eta Squared	P Value
Left Hippocampus					
Total volume	3239 (29)	3294 (27)	1.907	0.011	0.169
Hippocampal tail	506 (7)	535 (7)	8.243	0.046	0.005*
Presubiculum	294 (3)	308 (3)	8.471	0.047	0.004*
Subiculum	408 (5)	418 (4)	2.328	0.013	0.129
CA1	612 (7)	600 (6)	1.522	0.219	0.009
CA2/3	171 (3)	176 (2)	2.158	0.144	0.012
CA4	229 (3)	231 (2)	0.294	0.588	0.002*
GCL_DG	270 (5)	272 (3)	0.193	0.001	0.661
Fimbria	92 (2)	94 (2)	0.687	0.408	0.004*
Right Hippocampus					
Total volume	3217 (31)	3363 (29)	11.831	0.065	0.001*
Hippocampal tail	480 (8)	528 (7)	20.043	0.105	<0.001*
Presubiculum	270 (4)	294 (3)	24.365	0.125	<0.001*
Subiculum	395 (5)	420 (4)	15.172	0.081	<0.001*
CA1	638 (7)	639 (7)	0.017	0.000	0.896
CA2/3	179 (3)	191 (2)	10.995	0.060	0.001*
CA4	229 (3)	239 (2)	7.410	0.042	0.007
GCL_DG	270 (3)	281 (3)	6.542	0.037	0.011
Fimbria	97 (2)	89 (2)	10.563	0.058	0.001*

Abbreviations: * Significant after correction for multiple testing with Bonferroni method. P values are presented before Bonferroni correction. GCL_DG: Granule cell layer (GCL) of the Dentate Gyrus. Data presented include means and SEM.

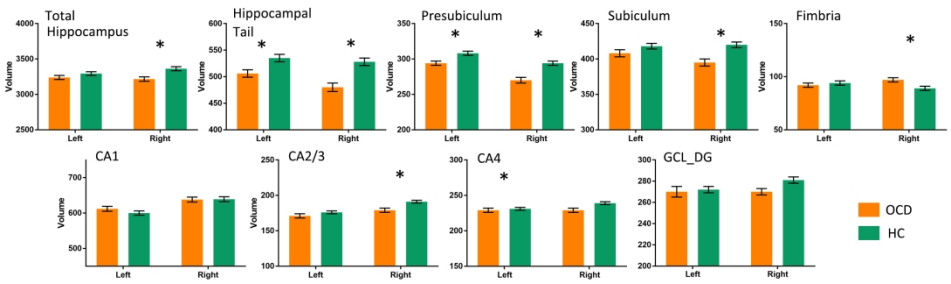

Figure 1. Bar chart of volumes of hippocampal subfields in patients with OCD compared with HC, adjusted for age, sex and ICV. *indicates significance after Bonferroni correction. Error bar indicates Standard Error. GCL_DG: Granule cell layer of the dentate gyrus.

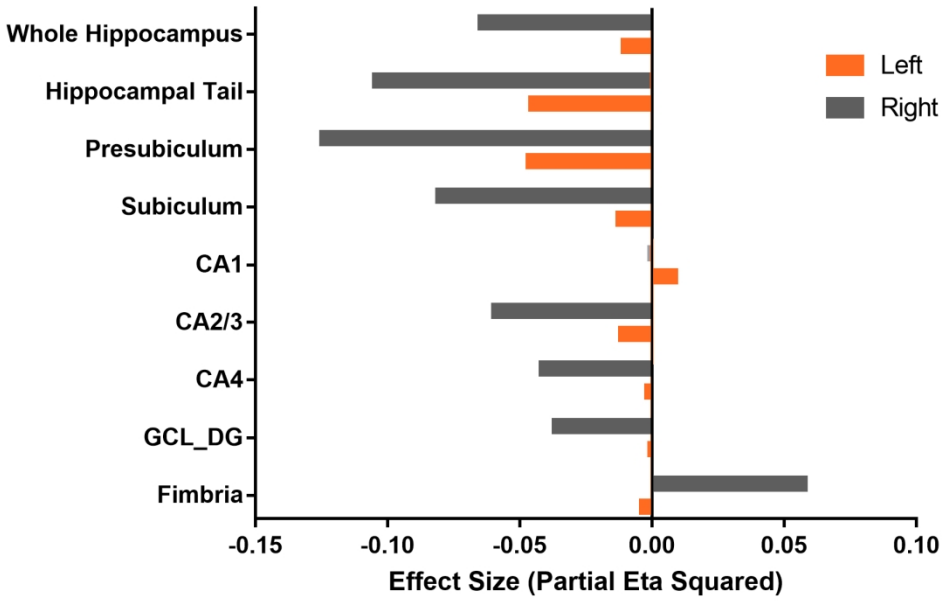

Figure 2. Effect sizes for differences in left (grey) and right (orange) hippocampal subfields between patients with OCD and HC subjects. GCL_DG: Granule cell layer of the dentate gyrus.

675x441mm (72 x 72 DPI)

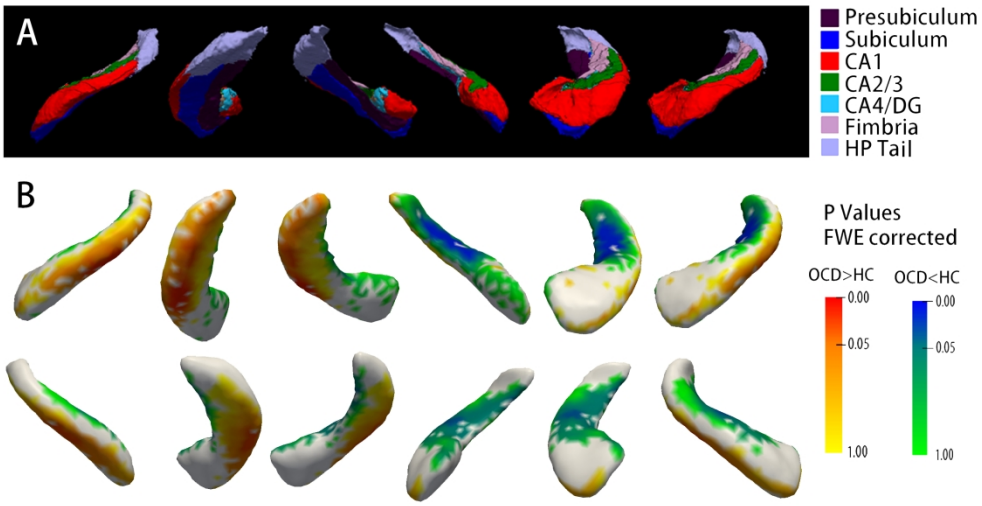

Figure 3. Vertex-wise comparison of hippocampal shape between patients with OCD and healthy individuals. A. An example of hippocampal subfield segmentation by FreeSurfer (v.6.0) in a healthy subject (left hippocampus is shown). B. Left (upper line) and right (lower line) hippocampus showed a lateral displacement in body/tail, and an outward bending in the middle/posterior portion of the structure. The p values presented are corrected for multiple testing with the family-wise Error (FWE) method.

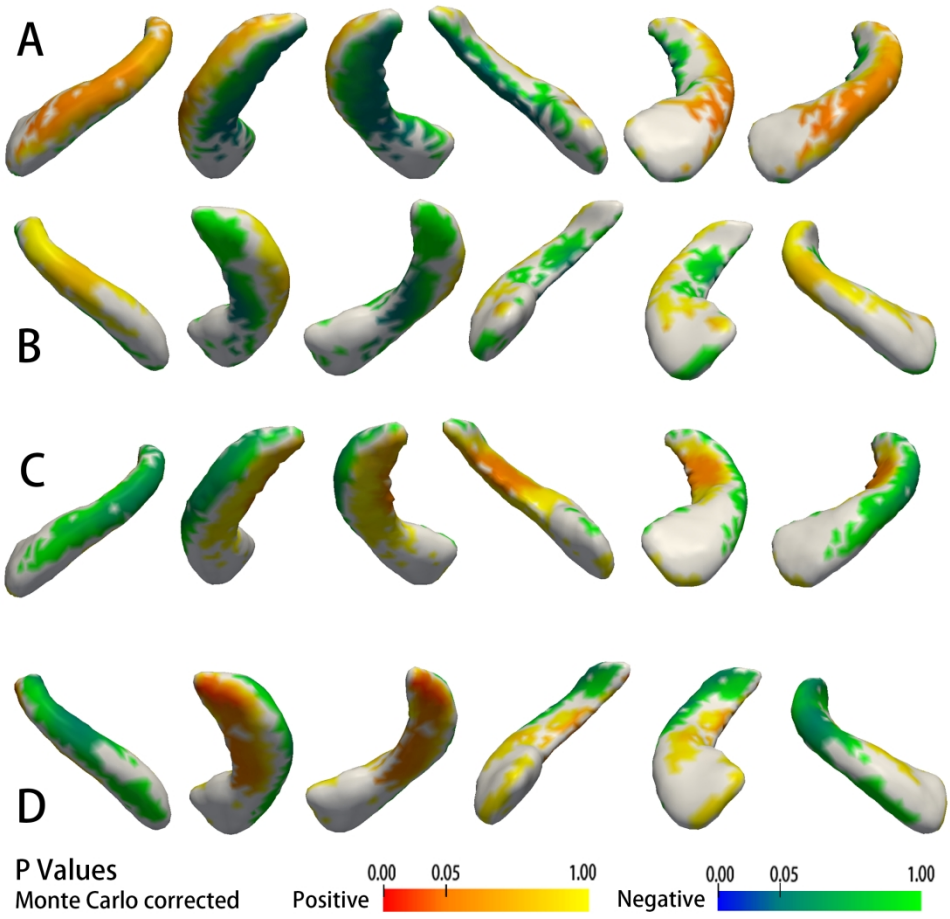

Figure 4. Vertex-wise correlation between compulsion and obsession ratings with regional shape deformity in hippocampus. Compulsions were positively correlated with lateral displacement of left (A) and right (B) hippocampus. Obsession scores were positively correlated with downward displacement of right (D) posterior hippocampus. Significance of correlations between left (C) hippocampal shape with symptom ratings did not survive Monte Carlo correction for multiple testing.